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ACINETOBACTER SUPERINFECTION IN ELDERLY COVID-19 PATIENTS WITH PNEUMOTHORAX – A REPORT OF TWO CASES

SUPERINFEKCIJA ACINETOBACTEROM KOD STARIJIH COVID-19 PACIJENATA SA PNEUMOTORAKSOM - PRIKAZ DVA SLUČAJA

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Summary

Introduction. Coronavirus disease 2019 is an infectious disease that primarily affects the lungs. Since the pandemic of severe acute respiratory syndrome coronavirus 2 continues and a large number of cases are registered worldwide, the knowledge about the virus and virus-related complications is growing as well. Pleural complications, pneumothorax, and empyema are important issues affecting better patient survival. Bacterial superinfections may cause complications of coronavirus disease 2019. Knowledge about the incidence of superinfections, microbiological causes, treatment, and outcomes of the disease is incomplete. **Case Report.** We present two oxygen-dependent patients with coronavirus disease 2019 who developed pneumothorax and empyema during hospitalization, three weeks after the onset of coronavirus disease 2019 symptoms. Multidrug-resistant Acinetobacter spp. was isolated from the thoracic drain. **Conclusion.** Pneumothorax may occur at any stage of coronavirus disease 2019 and is not always associated with the severity of viral infection. Empyema due to coronavirus disease 2019 pneumonia is rare and occurs as a superinfection of the pleural effusion. Excessive use of antibiotics in the treatment of hospitalized patients with coronavirus disease 2019 may increase the risk of nosocomial infections caused by multidrug-resistant bacteria.

Key words: COVID-19; Pneumothorax; Empyema; Pleural Effusion; Superinfection; Acinetobacter; Anti-Bacterial Agents; Drug Resistance, Bacterial; Risk Factors; Cross Infection

Sažetak

Uvod. Koronavirusna bolest 2019 je infektivna bolest koja prvenstveno pogađa pluća. Kako se pandemija teškog akutnog respiratornog sindroma *Coronavirus* 2 nastavlja i registruje veliki broj slučajeva širom sveta, znanje o samom virusu raste, kao i saznanje o komplikacijama. Pleuralne komplikacije, pneumotoraks i empijem važna su pitanja u vezi sa boljim preživljavanjem pacijenata. Bakterijske superinfekcije mogu zakomplikovati COVID-19. Saznanja o učestalosti superinfekcija, mikrobiološkim uzročnicima, lečenju i ishodu bolesti su nepotpuna. **Prikaz slučajeva.** Predstavljamo pacijente obolele od kovida, na kiseoničkoj terapiji, kod kojih se razvio pneumotoraks i empijem tokom hospitalizacije, nakon tri nedelje od početka simptoma infekcije koronavirusne bolesti 2019. Multirezistentni *Acinetobacter spp.* izolovan je iz brisa torakalnog drena. **Zaključak.** Pneumotoraks se može pojaviti u bilo kojoj fazi COVID-19 i nije uvek povezan sa težinom virusne infekcije. Empijem zbog COVID-19 pneumonije je redak i javlja se kao superinfekcija pleuralnog izliva. Prekomerna upotreba antibiotika u lečenju hospitalizovanih pacijenata sa COVID-19 može povećati rizik od bolničkih infekcija uzrokovanih multirezistentnim bakterijama.

Ključne reči: COVID-19; pneumotoraks; empijem; pleuralni izliv; superinfekcija; Acinetobakterija; antibiotici; bakterijska rezistencija na lekove; faktori rizika; unakrsna infekcija

Introduction

Over the last two years, since it was discovered in China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading rapidly around the world and is a major health problem even in the most advanced health systems. As the number of case studies about all types of SARS-CoV-2 and coronavirus disease 2019 (COVID-19) increases, so is the knowledge about the specifics of this disease and its complications [1]. The symptoms of COVID-19 typically include the respiratory system, but sometimes they present with abdominal pain, without findings of abdominal disease, and with no respiratory symptoms. Patients with diabetes, heart disease, hypertension, obesity, malignant diseases, and the elderly are at a greater risk of developing a severe clinical picture with complications [1–3].

The clinical symptoms in patients with COVID-19 pneumonia may range from asymptomatic to respiratory failure. The COVID-19 pneumonia may be complicated by pneumothorax, pleural effusion, pneumomediastinum, and empyema. Pneumothorax may be spontaneous, or it can be caused by barotrauma in patients on mechanical ventilation. Empyema due to COVID-19 pneumonia is rare and

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COVID-19	– coronavirus disease 2019
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
RT-PCR	– reverse transcription polymerase chain reaction
CT	– computed tomography
HFNO	– high-flow nasal oxygen
IV	– intravenous

occurs as a superinfection of the pleural effusion [4].

The bacterial superinfection of SARS-CoV-2 is more common than in other respiratory viral syndromes and it may be a determining factor in the disease evolution. According to different studies around the world, its prevalence ranges between 1% and 50% and leads to prolonged hospitalization, severe clinical picture, admission to the intensive care unit, mechanical ventilation, and other complications [5]. Excessive use of antibiotics in the treatment of COVID-19 hospitalized patients may increase the risk of nosocomial infections caused by multidrug-resistant bacteria.

We are presenting patients with pleural complications of COVID-19 pneumonia, pneumothorax and empyema with isolated Acinetobacter spp.

Case 1

A 62-year-old female with a history of hypertension, unvaccinated to SARS-CoV-2, was admitted to the Department of Infection Diseases, COVID department, in the General Hospital of Novi Pazar, Serbia, complaining of worsening dyspnea, fever, headache, malaise, and cough. The symptoms began about 10 days before admission when she underwent rapid antigen and reverse transcription polymerase chain reaction (RT-PCR) nasopharyngeal swab testing and was diagnosed with the novel COVID-19. The worsening of breathing with SpO_2 of 60% required hospitalization. Initial chest radiography showed bilateral pneumonia **(Figure 1)**.

The initial laboratory tests showed the following: C-reactive protein 99.8 mg/L, Interleukin 6 56.9 pg/ml, procalcitonin 0.09 μg/L, Lactate dehydrogenase 897 IU/L, Fe 4.3 μmol/L, Ferritin 720.44 ng/ml, Red Blood Cell count 4.1 x 10^{12}/L, White Blood Cell count 5.5 x 10^9/L, Platelets count 319 x 10^9/L, Hemoglobin 127 g/L, Hematocrit 0.37U/L, D dimer 2 mg/L.

The initial treatment included antibiotics (ceftriaxone, azithromycin), analgesics, proton pump inhibitors, corticosteroids, and other supportive therapy. Oxygen saturation was 95% at a rate of 15 l/min O_2 on nasal cannula. Due to the worsening of the respiratory condition, on day 6 of hospitalization, the patient was transferred to high-flow nasal oxygen (HFNO) therapy (fraction of inspired oxygen 100%, Flow 60 l/min) for the next 7 days. During the rest of hospital stay, she was on oxygen support, through a nasal mask up to 20 l/min with SpO_2 up to 94%. After a month of hospitalization, still oxygen-dependent, the patient presented with a severe pain in the right hemithorax. Chest X-ray and computed tomography (CT) showed a right pneumothorax **(Figure 2)**.

After a month from the initial positive test for SARS-CoV-2, according to the protocol, the patient was no longer considered infectious and the rapid antigen test for SARS-CoV-2 was negative, the patient was transferred to the Department of Surgery of our hospital, for further treatment. For the right pneumothorax treatment, Fr28 chest tube was inserted. After this intervention, lung re-expansion occurred **(Figure 3)**. Throughout the hospitalization, the patient required oxygen support up to 10 l with saturation up to 94%. On the repeated RT-PCR nasopharyngeal swab for SARS-CoV-2, the patient was still positive, after 35 days of hospitalization. Ten days after drainage, an attempt was made to remove the chest tube; it

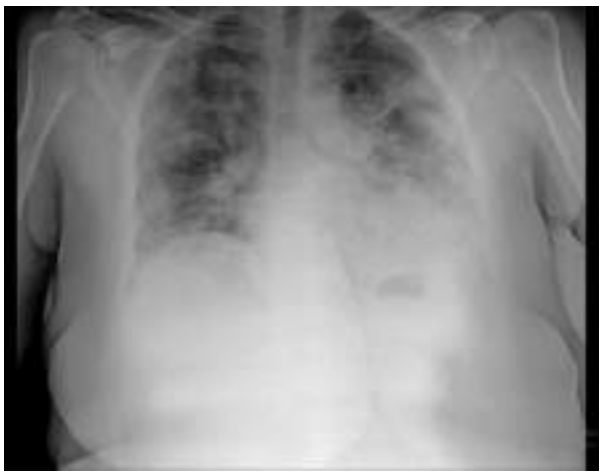

Figure 1. Multiple bilateral and diffuse confluent areas with predominantly peripheral localization indicating an advanced process of infectious etiology
Slika 1. *Bilateralne i difuzne višestruke konfluentne mrljaste senke pretežno periferne lokalizacije unutar uznapredovalog procesa infektivne etiologije*

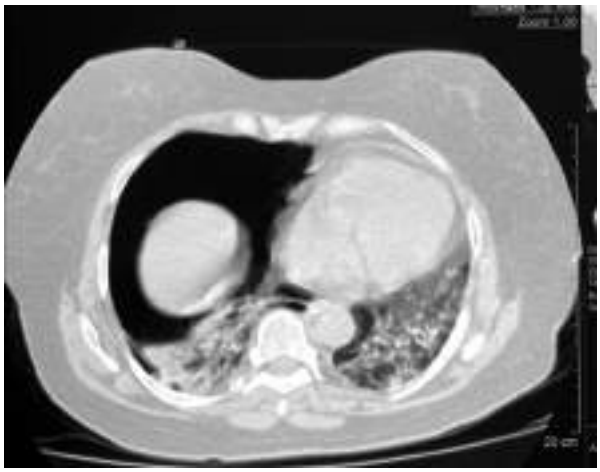

Figure 2. Right pneumothorax on chest CT after one month of hospitalization
Slika 2. *Desni pneumotoraks na snimku kompjuterizovane tomografije grudnog koša, nakon mesec dana hospitalizacije*

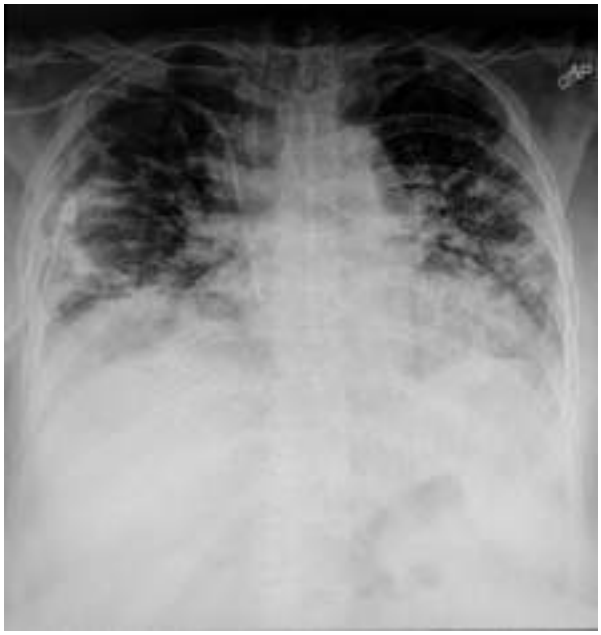

Figure 3. After chest drainage - pulmonary re-expansion
Slika 3. *Reekspanzija pluća nakon drenaže grudnog koša*

was not tolerated well, the saturation decreased and subcutaneous emphysema appeared, so the patient underwent redrainage. About 200 ml of liquid content was evacuated daily through the chest tube indicating the development of empyema. The initial swab was sterile. Due to the increase of inflammatory parameters and worsening of the general condition, the patient was transferred to a tertiary health institution, Thoracic Surgery, for further treatment.

Conservative treatment was continued. A control swab of the chest tube contents revealed Acinetobacter spp. sensitive only to imipenem and tigecycline. Blood cultures were sterile. Due to the general condition of the patient and the findings on the lungs caused by COVID-19 infection, conservative therapy was continued. Antibiotic therapy, according to the antibiogram, and supportive therapy were also continued. The patient responded well to the therapy.

The chest tube was removed on day 35 after insertion, and the patient was discharged for home treatment after 65 days of hospital stay.

Case 2

A 61-year-old female patient was admitted to our center presenting with shortness of breath, weakness, malaise, cough, nausea, and vomiting. The symptoms began 7 days before admission to the COVID Department, but got worse in the last 3 days. She was treated at home with antibiotics (azithromycin 500 mg twice a day and ceftriaxone 1 g/12/h IV), dexamethasone, integrated procedural platform, and supportive therapy.

The patient underwent surgery and radiotherapy for uterine cancer 2 years ago; she was treated for hypertension and was unvaccinated to SARS-CoV-2. Rapid serological test for SARS-CoV-2 (IgM and IgG negative), rapid antigen, and RT-PCR nasopharyngeal swab

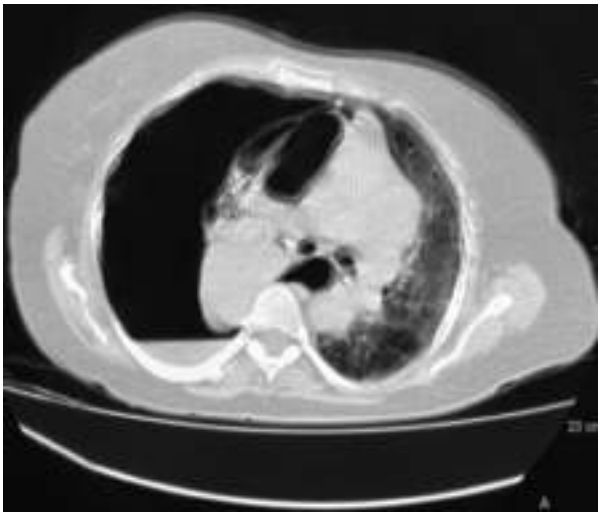

Figure 4. Right pneumothorax on a chest CT
Slika 4. *Desni pneumotoraks na snimku kompjuterizovane tomografije grudnog koša*

were positive. On admission, the patient presented with cyanosis, dyspnea and hypertension; she was afebrile with oxygen saturation of 52% and after application of oxygen 30 l/min the SpO_2 was 88%.

The initial laboratory test results were as follows: Interleukin-6 1120 pg/ml, C-reactive protein 230 mg/L, procalcitonin 0.08 µg/L, ferritin 697 ng/ml, Lactate dehydrogenase 1252 IU/L, Fe 3.8 µmol/L, Red Blood Cell 4.07 x 10^{12}/L, White Blood Cell 9.7 x 10^9/L, PLT 328 x 10^9/L, Hemoglobin 122 g/L, Hematocrit 0.35 U/L, D dimer 2.4 mg /L.

The chest X-ray showed a zone of incomplete consolidation in the lower field of the right lung and in the rest of the lung parenchyma there were multiple shadows of inflammatory etiology. During the first 13 days of hospitalization, the patient received HFNO (FiO_2 100%, flow 60 l/min). After that, she was on oxygen therapy through the nasal mask up to 15 – 20 l/min with SpO_2 up to 95%.

The patient was treated with conservative therapy: proton pump inhibitors (IPP), probiotics, fluids, antibiotics, corticosteroids, low-molecular-weight heparins (nadroparin calcium 0.6 mL/12 h), biological therapy - tocilizumab 8 mg/kg IV in two doses.

Mild regression of radiologically verified COVID-19 pneumonia occurred with the prescribed therapy. After 3 weeks of hospitalization, the patient presented with an increase in IL 6 (> 1000) and WBC (23.3) and right hydropneumothorax was established **(Figure 4)**. The patient was transferred to the Department of Surgery for further treatment. Chest tube Fr28 was inserted in the right hemithorax. After this intervention, lung re-expansion occurred **(Figure 5)**. The first three days after drainage, about 1600 ml of liquid content was extracted through the chest tube. Due to the worsening of the general condition and inflammatory parameters, the patient was transferred to a tertiary health institution, Thoracic Surgery Department for further treatment. A control swab of the chest tube

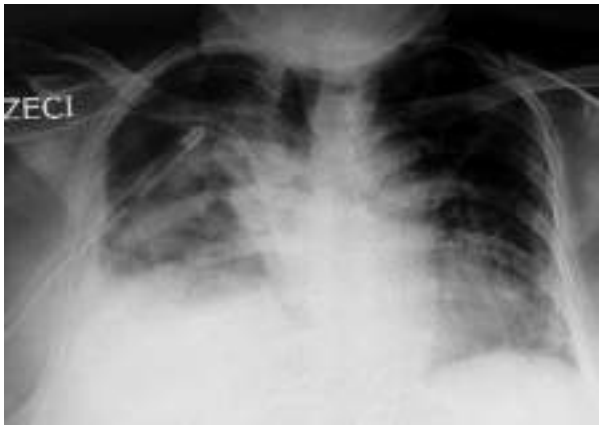

Figure 5. After chest drainage - pulmonary re-expansion
Slika 5. *Reekspanzija pluća nakon torakalne drenaže*

contents and blood cultures revealed Acinetobacter spp. sensitive only to tigecycline.

The patient did not respond well to the therapy and her condition was deteriorating. Apart from poor inflammatory parameters and general condition, she developed a septic infection that led to a lethal outcome on day 52 after the onset of COVID-19.

Discussion

According to the etiology, pneumothorax can be classified as spontaneous and traumatic. Secondary spontaneous pneumothorax occurs in patients with underlying lung disease [6].

Pneumothorax is an important complication of COVID-19 that is associated with increased mortality, morbidity, and health care costs [2, 7]. The data about the incidence of pneumothorax in COVID-19 patients are mostly obtained through published case reports of patients with COVID-19 with pneumothorax, and therefore it is unknown. Marciniak et al. found an incidence of 0.91% in COVID-19 patients. Similar results were reported by Chen et al. with 1% [8] and 2% of patients requiring intensive care unit admission in other studies [8–10]. Martinelli et al. also found that 1% of patients admitted with COVID-19 develop pneumothorax and this can occur without a pre-existing lung disease or mechanical ventilation [11]. It seems that it mostly affects males; patients who require noninvasive or invasive ventilatory support are at a higher risk [7].

The precise pathogenesis of pneumothorax in patients with COVID-19 has not been fully elucidated. According to the literature, parenchymal lung damage in COVID-19 with ischemic and inflammatory effects may increase the incidence of pneumothorax, such as surfactant changes, loss of extracellular matrix and basement membrane in COVID-19-infected lung tissue, or pulmonary cyst rupture. Coughing has also been associated with pneumothorax via the Macklin effect [12, 13].

Both of our patients were elderly females, nonsmokers, without previous lung disease, critically ill and both were on HFNO and prolonged oxygen therapy.

Empyema developing in COVID-19 pneumonia is rarely reported in the literature. Tessitore et al. reported that a strong inflammatory response causes reactive pleural effusion and empyema with bacterial superinfection [14]. This is confirmed by other authors (2 – 14). The COVID-19 infection may predispose to secondary bacterial infection which is associated with poor clinical outcomes, especially among critically ill patients. In contrast to other coronaviruses, SARS-CoV-2 has been associated with an increase in secondary bacterial infections. Several studies have reported that a variable percentage of COVID-19 patients (4 – 20%) have bacterial and/or fungal co-infection. In recent meta-analysis, bacterial co-infection was reported in 7% of hospitalized patients with COVID-19 and up to 14% in critically ill patients or those with secondary infection [15–17].

The empiric use of antibiotics in a great number of hospitalized patients with COVID-19 is reported in many studies. It is shown that the inflammatory markers, such as increased levels of procalcitonin and C-reactive protein, which are usually associated with bacterial infection, may appear without an existing bacterial co-infection in COVID-19 patients [17]. Fan et al. observed that lung microbiota of deceased patients with COVID-19 exhibited complex bacterial and fungal colonization by opportunistic species [18]. Excessive and uncritical use of antibiotics in the treatment of these patients, as well as long-term hospitalization, with or without mechanical ventilatory support, may lead to superinfection of nosocomial bacterial strains resistant to most antibiotics. In the study of Clansy et al., potential bacterial lung superinfections were evident at postmortem examination in 32% of persons who died of COVID-19. They also noted that 3.5% of patients had empyema, and lung superinfections were the cause of death in 3% of all patients with COVID-19 [19]. Yet, despite the increasing number of COVID-19 studies, the predisposition of COVID-19 patients to secondary infection is not fully understood [15]. Our data are in accordance with the literature data.

Acinetobacter spp. has been implicated in nosocomial infections of clinical importance in the elderly, infants, and immune-compromised patients. Acinetobacter spp. infections lead to high mortality and morbidity, prolonged hospital stay with high treatment costs.

Although most Acinetobacter species are nonpathogenic, they are an important reservoir of antibiotic resistance. Multidrug-resistant Acinetobacter is a major concern in hospitals in many parts of the world. Olu-Taivo et al. found 62% resistance to at least three or more antimicrobial agents [20]. This is in line with previous reports from Italy (54%) and the United States (72%) [21, 22]. Both of our patients were treated with antibiotics for a long

period of time and the isolated Acinetobacter was resistant to almost all antibiotics.

Conclusion

Pulmonary complications in hospitalized patients with coronavirus disease 2019 increase the mortality rate and the development of more severe clinical forms of the disease. Extensive and long-term use of antibiotics may increase the incidence of nosocomial superinfections. Further researches are needed to better understand this disease.

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